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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	ART UNIT	PAPER NUMBER
HAUDA M. A	1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/704,445	Applicant(s) Chen et al.
	Examiner Karen M. Hauda	Group Art Unit 1632

☒ Responsive to communication(s) filed on *March 23, 1998 and July 31, 1998* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-3, 5, and 7-35* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-3, 5, and 7-35* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's response filed March 23, 1998 and July 31, 1998 have been entered. Claims 1-3, 5 and 7-35 are pending.

The prior rejection of claim 1-23 and 31 under 35 USC § 112, second paragraph is withdrawn in view of applicant's amendment filed July 31, 1998.

The prior rejection of claims 1-17 and 19-23 under 35 USC § 103, as being obvious over Adrovandi, Pinto, Pflumio and Kuby is withdrawn in view of applicant's amendment filed March 23, 1998 and July 31, 1998.

The prior rejection of claims 24-30 under 35 USC § 103, as being obvious over Berenson and Baum taken with Pinto, Pflumio and Kuby is withdrawn in view of applicant's amendment filed March 23, 1998 and July 31, 1998.

Applicant's arguments are rendered moot in view of withdrawal of all prior rejections. New grounds of rejection as they pertain to the currently pending claims are set forth below.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

Claim Rejections - 35 USC § 112

Claims 1-3, 5 and 7-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing the depletion of non-autologous hematopoietic cells in a mammal which lacks functional endogenous B- and T- cells comprising administering to the mammal an effective amount of dichloromethylene diphosphonate such that

the number of endogenous macrophages are decreased to a level effective to reduce depletion of transplanted non-autologous hematopoietic stem cells, does not reasonably provide enablement for a method of reducing depletion in any and all mammals of non-autologous hematopoietic cells comprising administering to the mammal an effective amount of any agent which selectively decreases the number of endogenous macrophages to a level effective to reduce depletion of non-autologous hematopoietic cells (or methods of restoring or improving engraftment efficiency for transplantation comprising the same methodology- claims 24 and 31). Additionally, the specification while being enabled for a non-human mammal which lacks functional endogenous T- and B- cells comprising human hematopoietic cells wherein the non-human mammal contains a decreased level of endogenous macrophages sufficient to reduce depletion of non-autologous hematopoietic cells, wherein the decreased level of endogenous macrophages is achieved by administering to the mammal an effective amount of dichloromethylene diphosphonate, does not reasonably provide enablement for any non-human mammal comprising human hematopoietic cells wherein the mammal contains a decreased level of endogenous macrophages sufficient to reduce depletion of non-autologous hematopoietic cells, wherein the decreased level of endogenous macrophages is achieved by administering to the mammal an effective amount of any agent which selectively decreases the number of endogenous macrophages. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's specification provides working examples which exemplify an improvement in tolerance for non-autologous human hematopoietic cells transplanted into SCID-hu Thy/Liv mice when endogenous macrophages were depleted by the administration of dichloromethylene diphosphonate (Cl_2MDP) (see Examples in specification). It was well settled in the art at the time of the claimed invention that T-cells and B-cells play an important role in graft tolerance and rejection. This is supported by the teachings of Kuby (see paragraph bridging page 488-489, previously cited), Bosma et al. (see page 341-343, for example, previously cited), Sykes et al. (Seminars in Immunology, 1990, see entire article, especially pages 408-409) and Smith et al. (Transplantation Proceedings, 1991, see entire article). Applicants invention is directed to the discovery that reduction or elimination of endogenous macrophages in a host improves the tolerance of non-autologous hematopoietic cells. However, applicant's claims are not commensurate in scope with the enabled embodiments of the specification. While applicants have clearly shown that reducing or eliminating endogenous macrophages improves tolerance to non-autologous hematopoietic cells in mammals which lack functional endogenous T- and B-cells, there is no support or evidence within applicants specification that the elimination of endogenous macrophages improves tolerance to non-autologous hematopoietic cells in mammals which have functional T- and B- cells. Given what was known in the art regarding the strong role of T- cells in graft rejection, one of skill in the art would not correlate the findings as exemplified in applicants specification to mammals with functional T- and B-cells. In fact it is unlikely that macrophages play a stronger role in graft rejection than T-cells, such that elimination of

macrophages alone would reduce the depletion of transplanted non-autologous hematopoietic cells due to the known MHC incompatibility and the role that T-cells have in rejecting MHC incompatible cells (see Sykes and Smith as referenced above). It is noted that although some of applicants claims recite immunosuppression by either chemotherapy, radiation therapy, or HIV infection. With the exception of whole body irradiation, these treatment modalities would not always render all T- and B-cells non-functional. In fact depending on the course of treatment, the patient may have most of their T- and B-cells functional. The examples provided in the specification could not be correlated with standard immunosuppression unless it was demonstrated that T-cells and B-cells were rendered completely non-functional by these methodologies. While irradiation and chemotherapy can be used to render T-cells and B-cells non-functional, such is not a limitation of the claim language. Additionally, it is noted that whole body irradiation would deplete all macrophages as well as T- and B-cells, such that selective depletion using an agent would be impracticable. Therefore, it would have required undue experimentation for one of skill in the art to practice the claimed invention for the scope claimed due to the unpredictability of tolerizing mammals with functional endogenous T- and B-cells to non-autologous hematopoietic cells, the state of the art to the known role of T-cells rejecting grafts, the absence of working examples for embodiments of the claimed invention wherein the recipient mammal contains functional T- and B- cells, the nature of the transplantation art in general, and the breath of the claims.

Additionally, applicants claimed invention encompasses methods of reducing depletion in a mammal with any and all reagents which "selectively" decreases the number of endogenous macrophages, however, the specification only provides embodiments of a single agent, that of Cl_2MDP, which is known to selectively reduce macrophages. No other reagents are specifically disclosed in the specification. While one of skill in the art could imagine antibodies to be encompassed within this embodiment, antibodies specific to macrophages are not known in the art and applicants have not provided guidance to the skilled artisan on how one of skill in the art could obtain such reagents. In fact, applicants detection of macrophages as disclosed in the specification was by histological staining. It would have required undue experimentation for one of skill in the art to identify a reagent (other than Cl_2MDP) and determine its concentration for use *in vivo* such that it would selectively deplete endogenous macrophages in any and all mammalian species given the absence of teaching in applicants specification, the absence of known reagents in the art, the unpredictability of isolating a reagent which would selectively decrease endogenous macrophages in any and all mammals without undue experimentation, the breadth of the claims, and the quantity of experimentation which would be required to identify such a reagent.

Therefore, for the reasons presented above, the claimed invention is limited to a method of reducing the depletion of non-autologous hematopoietic cells in a mammal which lacks functional endogenous B- and T- cells comprising administering to the mammal an effective amount of dichloromethylene diphosphonate such that the number of endogenous macrophages are decreased to a level effective to reduce depletion of transplanted non-autologous hematopoietic

stem cells; a non-human mammal which lacks functional endogenous T- and B- cells comprising human hematopoietic cells wherein the non-human mammal contains a decreased level of endogenous macrophages sufficient to reduce depletion of non-autologous hematopoietic cells, wherein the decreased level of endogenous macrophages is achieved by administering to the mammal an effective amount of dichloromethylene diphosphonate; and a method of improving or restoring engraftment efficiency for transplantation of a population of non-autologous hematopoietic cells in a host mammal which lacks functional endogenous T- and B- cells comprising transplanting non-autologous hematopoietic cells into a T- and B- cell deficient mammal in conjunction with administering to the mammal an effective amount of dichloromethylene diphosphonate which selectively decreases the number of endogenous macrophages in the host mammal.

Claims 1-3, 5, 7-18, 28 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it appears to be either incomplete or is rendered confusing based on dependent claims. Claim 1 recites "A method of reducing depletion of non-autologous hematopoietic cells comprising administering to the mammal an effective amount of an agent which selectively decreases the number of endogenous macrophages to a level..." Claim 1 as recited does not contain a step of administering non-autologous hematopoietic cells to the

mammal, such that in reading claim 1 independently the mammal treated with the agent contains non-autologous hematopoietic cells. However, claims 2, 3, 14, and 15, recite how the non-autologous hematopoietic cells are introduced into the mammal, which appears to indicate that claim 1 is incomplete because it lacks an administration step for hematopoietic cells. If claim 1 is not incomplete, claims 2, 3, 14 and 15 are irrelevant because it does not matter how the cells are transplanted into the mammal that already contained the hematopoietic cells. To make sense of claims 2, 3, 14 and 15 it would appear that applicants are further transplanting or injecting the mammal with hematopoietic cells. It is further noted that claim 1 is even more confusing when claims 13 and 17 are compared, because claim 13 encompasses a mammal which contains non-autologous hematopoietic cells and claim 17 does not. Clarification of the intended claim language is necessary. Note, claims 2, 3, 5 and 7-17 depend from claim 1.

Claim 3 is further indefinite because it recites "the cells", however these cells could refer to non-autologous hematopoietic cells (the intention) or to macrophages as recited in claim 1. For clarification, it is suggested that the phrase "non-autologous hematopoietic" be placed in front of the term "cells".

Claim 18 is indefinite because it recites "the animal" on line two, which lacks antecedent basis. It is suggested that "animal" be replaced with the term "mammal".

Claim 28 is indefinite because it contains a period after the first occurrence of the term "cells". Note, the amendment filed December 22, 1995, paper # 9, did not specify where the

period should be inserted, such that it was inserted after the first occurrence of the term "cells". Correction is necessary.

Claim 31 is indefinite because the phrase "the host animal" on line 5 lacks antecedent basis. It is suggested that the term "mammal" be replaced with the term "animal". Claim 31 is additionally indefinite because the term "number" on line 7 is misspelled as "numer". Correction is necessary.

Claims 1-3, 5 and 7-35 are free of the prior art, because the prior art does not teach or suggest that selective depletion of macrophages would reduce depletion of non-autologous hematopoietic cells administered to a mammal.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen M. Hauda whose telephone number is (703) 305-6608.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian R. Stanton, may be reached at (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-2801.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Papers related to this application may be submitted to Group 160 by facsimile transmission. Papers should be faxed to Group 160 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

Karen M. Hauda

Karen M. Hauda
Patent Examiner
October 9, 1998